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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,405	10/28/2003	Johanna Bentz	3139-6328.1US (ARC 3277 U	7380

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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
05/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/696,405	BENTZ ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-16 and 30-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-16 and 30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/17/08 has been entered.

Response to Amendments

Applicant's amendments filed 3/17/08 to claim 30 have been entered. Claims 17 and 19-29 have been cancelled in this reply. No claims have been added. Claims 1-12, 14-16, and 30-35 remain pending in the current application, all of which are being considered on their merits. Prior art references not included with this Office action can be found in a prior action.

Election/Restrictions

Applicant's election without traverse of various species, including "pituitary adenylate cyclase polypeptide (PACAP)" as the polypeptide and "amino acid buffers" as the buffers in the reply filed on 10/30/06 is still in effect over the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12, 14-16, and 30-35 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Carpenter et al. (1989, U.S. Patent 4,806,343), Andya et al. (2001, U.S. Patent 6,267,958), Thomson (1989, U.S. Patent 4,816,440), Nishimura et al. (1999, U.S. Patent 5,861,284), and Arimura et al. (1992, U.S. Patent 5,128,242).

Carpenter et al. teach a composition comprising phosphofructokinase (PFK), a polypeptide; trehalose; and zinc ions, said composition being lyophilized to form a powder that stabilizes the activity of PFK (Example VII; column 6, lines 30-47). Specifically, the composition of Carpenter et al. comprises an aqueous solution of 0.025mg/mL PFK, 0.32mM $ZnSO_4$ (0.051mg/mL), and 60mM trehalose (20.5mg/mL). Therefore, the weight ratio of metal ion to polypeptide is 2.04:1, which is "about" 1:1, "about" 2:1, and "about" 4:1. The zinc ion in the composition of Carpenter et al. is "derived" from $ZnCl_2$ (as in claim 9) in that zinc chloride ionizes in water to yield zinc ion;

the claim does not require that the recited divalent salts *per se* be present in the composition.

. Carpenter et al. do not teach a composition in which the polypeptide is PACAP or any other polypeptide selected from the pituitary adenylate cyclase polypeptide/glucagon superfamily. Carpenter et al. do not exemplify the ratios of trehalose to PFK recited in claims 5-7. Carpenter et al. do not exemplify a lyophilized composition comprising each and every metal ion recited in claim 9. Carpenter et al. do not teach a composition in which the surfactant is SDS

Andya et al. teach compositions comprising a protein, e.g. HER2 antibody; trehalose, a sugar; TWEEN 20, a surfactant; and in some cases, histidine, an amino acid buffer, said composition being lyophilized to form a powder that stabilizes the activity of HER2 antibody (column 2, lines 4-41; Table 2, lines 7-14). Specifically, the compositions of Andya et al. comprise 21mg/mL HER2 antibody, 250mM trehalose (86mg/mL), 0.01% or 0.2% TWEEN 20 (10 or 200mg/mL), and 10mM histidine (1.55mg/mL). The lyophilized formulation of Andya has an acidic pH since it is prepared in an acidic buffer (column 15, lines 1-10), and it may be reconstituted in any diluent, including buffers that may be acidic (column 17, lines 22-39).

Thomson teaches a composition comprising lyophilized interleukin-2, which is stable (column 9, lines 37-45). Thomson also teaches a lyophilized composition comprising interleukin-2 or interferon-beta and SDS (column 3, lines 30-39).

Nishimura et al. teach a composition for stabilizing polypeptides with an amide at their C-terminal or a disulfide linkage in the molecule, one of which is PACAP (column

4, lines 39-56, particularly lines 51-52). The composition of Nishimura et al. is lyophilized, *i.e.* it is a powder comprising particles (column 12, lines 53-63) and may further comprise trehalose (column 12, lines 23-26) as well as buffers, salts, and/or surfactants (column 12, lines 49-53).

Arimura et al. teach that PACAP and fragments thereof have therapeutic activity, for example in stimulating the pituitary (column 6, section 5.3 starting at line 45).

A person of ordinary skill in the art would have had a reasonable expectation of success in including an amino acid buffer and/or a surfactant in the composition of Carpenter et al. because Andya et al. teach that amino acid buffers and surfactants may be included in lyophilized compositions comprising any of numerous diverse proteins. The selection of the pH of the composition would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Andya et al. teach making their formulation using an acidic buffer and also teach that the formulation may be reconstituted in any of several buffers, any of which may be acidic. The skilled artisan would have been motivated to include amino acid buffers and/or surfactants to yield a composition with acidic pH either in the dry or reconstituted form because Andya et al. teach that such molecules protect the protein during the lyophilization and storage processes and that acidic preparations maintain their stability (see the Figures).

The selection of the amount of trehalose, metal ion, amino acid buffer, and/or surfactant to add to the composition of Carpenter et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing

that Carpenter et al. teach that the amount may be modified as necessary (column 3, lines 19-35). Furthermore, Andya et al. broadly teaches that proteins may be lyophilized with varying amounts of trehalose as necessary. A holding of obviousness over the cited claims is therefore clearly required.

The selection of the metal ion to include the composition of Carpenter et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Carpenter et al. teach that the addition of calcium, magnesium, or zinc increases the activity of PFK in the composition compared to compositions lacking such metal ions (Example III; Table I; column 5, lines 5-31). A holding of obviousness over the cited claims is therefore clearly required.

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the SDS of Thomson for the surfactants of Andya et al. because Thomson teaches that SDS, like the surfactants of Andya et al., protect proteins from lyophilization. The skilled artisan would have been motivated to make this modification because Thomson teaches that SDS maintains the stability of lyophilized proteins.

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the PACAP of Nishimura et al. for the PFK of Carpenter et al. because Nishimura et al. teach that PACAP, like PFK, can be stably stored by lyophilizing a solution of the protein, trehalose, and salts; furthermore, Andya et al. teach that a diverse group of proteins can be preserved in such a compostion. The skilled artisan would have been motivated to make this substitution in order to preserve

active PACAP, which Arimura et al. teach is a therapeutic protein for pituitary disorders, until it is needed to treat a patient.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to include acidic amino acid buffers and/or surfactants in the composition of Carpenter et al. because Andya et al. teach that, like trehalose and metal ions, acidic amino acid buffers and surfactants are lyoprotectants. It is well established that duplicating components with similar functions within a composition is obvious; see *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) and M.P.E.P. § 2144.04. It would have been further obvious to modify the amount of trehalose, metal ion, amino acid buffer, and/or surfactant and the character of the metal ion included in the composition of Carpenter et al. because Carpenter et al. and Andya et al. suggest such optimization.

It would have been further obvious to a person of ordinary skill in the art at the time the invention was made to substitute the SDS of Thomson for the surfactants of Andya et al. because the two are functional equivalents, *i.e.* they protect proteins in lyophilized compositions. Therefore, these may be considered to be art-accepted equivalents.

It would have been further obvious to a person of ordinary skill in the art at the time the invention was made to substitute the PACAP of Nishimura et al. for the PFK in the composition of Carpenter et al. because Arimura et al. teach that PACAP is a valuable therapeutic biomolecule, and because Nishimura et al. teach that PACAP can be preserved in a composition similar to that of Carpenter et al.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that the art does not suggest optimizing the pH in an acidic range and that the compositions of the prior art do not have an acidic reconstitution pH (Reply, page 9, paragraphs 1 and 2). These arguments have been fully considered, but they are not persuasive.

As discussed above, the lyophilized composition of Andya et al. may be prepared using histidine buffer at pH 4-8 or, preferably, pH 5-7; this is an acidic pH. In any case, as has been discussed in previous Office actions, the claims do not require that the stabilized particles being claimed have an acidic pH, only that they yield a solution of acidic pH when reconstituted under some unnamed conditions. Paragraph 28 of the specification (cited by applicant) does not make any connection between the pH of the composition per se and the pH upon reconstitution. In other words, the claims attempt to describe a composition by properties it exhibits after being subjected to downstream applications. In any case, Andya et al. teach that lyophilized proteins may be reconstituted using buffered solutions. The combined teachings of the cited prior art indicate that the selection of the pH (including the selection of alkaline or acidic conditions within the composition and in the reconstitution medium) would have constituted routine optimization at the time of the invention. Applicant has provided no evidence to the contrary. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651